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Pattern of Distribution of Intraductal and Infiltrating Ductal Carcinoma: A Three-Dimensional Study Using Serial Coronal Giant Sections of the Breast

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The purpose of this study was to establish the 3-dimensional (3D) structure of the breast tissue and to study the distribution and relationship between the intraductal and infiltrating components of ductal carcinoma and other proliferative epithelial lesions of the breast. Thirty mastectomy specimens with infiltrating carcinoma less than 3.0 cm in diameter were serially cut in the coronal plane. Each giant section was divided into small sections for routine processing. Using Photoshop (Adobe) and PowerPoint (Microsoft) software programs, the routinely stained sections were scanned and assembled to reestablish complete giant sections of the breast and subsequently the 3D structure. Intraductal and infiltrating ductal carcinomas, epithelial hyperplasia with atypia, and marked epithelial hyperplasia without atypia were mostly confined to a single duct (27 cases), resulting in an increase in size of the involved breast segment. Three remaining cases included a case of Paget's disease with tumor appearing to spread from one duct system to another system through the epidermis and two cases with multiple separate foci of carcinomas located in different quadrants and accompanied by ductal spread in different lactiferous ducts. Both intraductal and infiltrating carcinomas were often located in the superficial segments (near the subcutaneous tissue) (28 cases). The infiltrating components were often located adjacent to area of pure intraductal carcinoma and were often peripheral (nearer the chest wall than the nipple). Intraductal carcinomas showed a "fanned out" pattern of distribution, frequently extended toward the nipple (with involvement of the nipple or subareolar tissue in 7 cases), and occasionally were seen in the breast tissue peripheral to the infiltrating carcinoma. Multiple ducts with intraductal carcinoma could be seen to be connected with each other with serial sections. However, in at least 6 cases, foci of intraductal carcinomas were separated from each other by segments of duct with benign epithelium. Breast carcinoma often arise from the breast segment close to the subcutaneous tissue. Infiltrating carcinoma lesser than 3.0 cm in diameter is usually located adjacent to the area of pure intraductal. The pattern of spread of intraductal carcinoma has a pyramid-like shape, with the summit toward and occasionally extending up to the nipple. These findings should be considered in the surgical strategy for segmental resections of breast carcinomas. HUM PATHOL 31:464-474. Copyright © 2000 by W.B. Saunders Company

Key words: **breast, DCIS, infiltrating ductal carcinoma, three-dimensional, ductal spread.**

Abbreviations: **DCIS, ductal carcinoma in situ; AH, atypical epithelial hyperplasia; EH, epithelial hyperplasia without atypia; 3D, 3-dimensional; IC, infiltrating carcinoma.**

Infiltrating ductal carcinoma of the breast is often associated with ductal carcinoma in situ (DCIS), atypical epithelial hyperplasia (AH), and epithelial hyperplasia without atypia (EH).[1-8] The distribution in the breast and topographic relationship of these lesions with a 3-dimensional (3D) microscopic examination have been reported in studies based on sub-gross examination,[9-12] combined historadiographic comparison,[13] stereomicroscopic analysis,[14,15] and serial sections.[16-22] In these studies, the examination was limited to certain types of lesions or was performed on parallel serial sections taken at random directions. In this study, we examined the breast specimens containing in situ and infiltrating ductal carcinoma by the use of serial coronal sections to create a 3D microscopic structure of the breast. This enables us to study the pattern of DCIS spread and the geographic relationship between infiltrating ductal carcinoma, DCIS and other proliferative epithelial lesions.

MATERIALS AND METHODS

Mastectomy specimens performed for ductal carcinoma, previously diagnosed by fine-needle aspiration biopsy or core needle biopsy, were examined in the fresh state at the Anatomical Pathology Laboratory of the Ottawa Hospital—Civic Campus. Cases of infiltrating lobular carcinoma were excluded from the study. The fresh specimens were serially cut into 0.5-cm-thick coronal sections (parallel to the fascia of the thoracic wall). A relatively even thickness of the sections was achieved by using a sharp long-bladed knife for areas of breast consisting predominantly of fibrous tissue. For predominantly fatty areas, however, it was necessary to cut the fatty tissue by using a scalpel to avoid producing holes in the slice. After obtaining tumor samples for biochemical assay of estrogen and progesterone receptor (in cases of carcinoma greater than 1 cm in diameter), sections were placed on a flat surface and fixed in 10% buffered formalin. After 12 to 60 hours' fixation (the predominantly fatty breast required longest period of fixation) that caused tissue shrinkage, the tissue was trimmed into giant sections of 3 mm thickness. Every second giant section was divided into small sections for routine processing and staining with hematoxylin-phloxin-saffron (Fig 1). The site and the orientation of each section were recorded and marked with ink or knife mark. Additional routine sections were also taken to establish a complete 3D structure

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0046-8177/00/3104-0011$10.00/0
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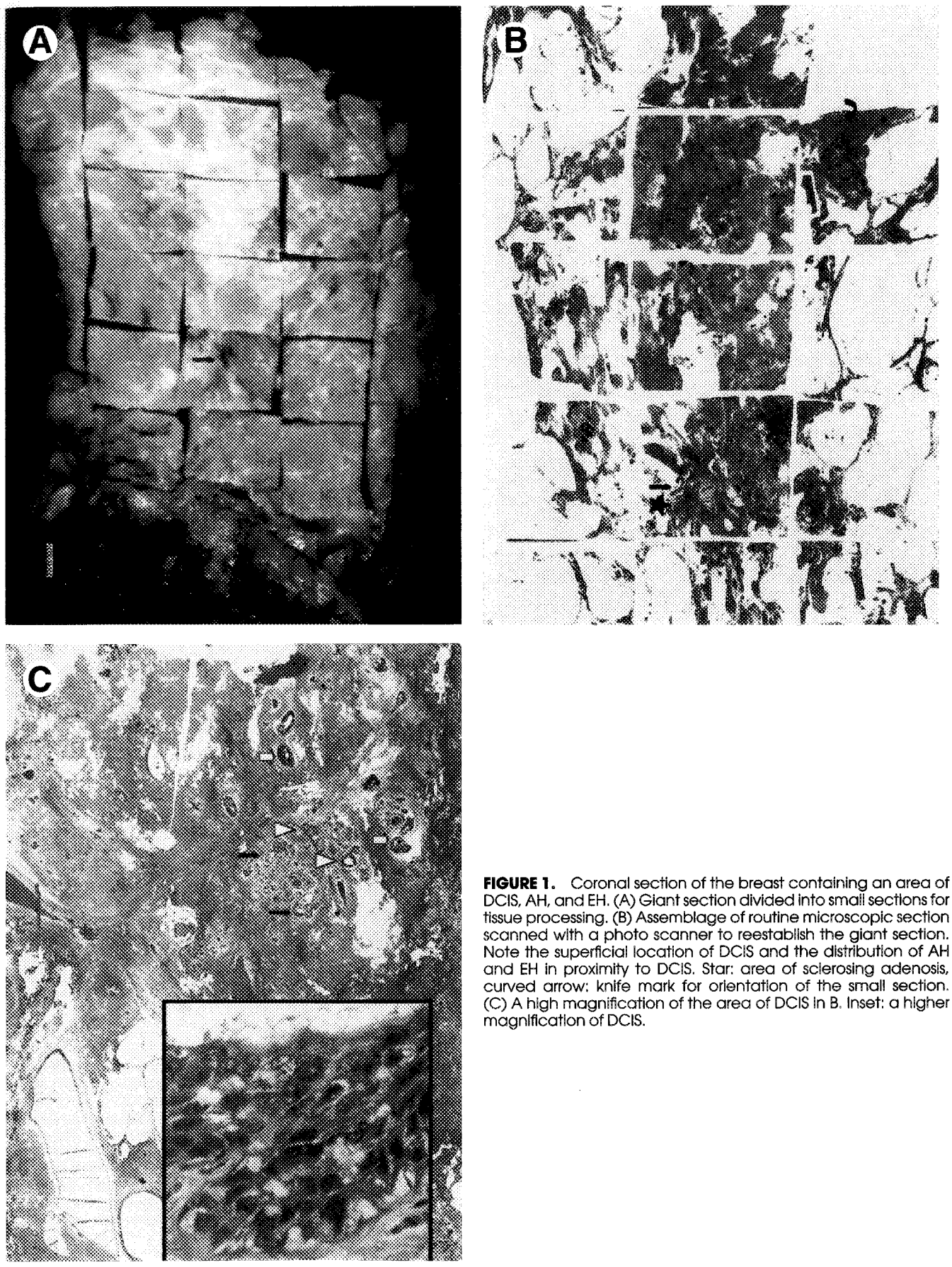

FIGURE 1. Coronal section of the breast containing an area of DCIS, AH, and EH. (A) Giant section divided into small sections for tissue processing. (B) Assemblage of routine microscopic section scanned with a photo scanner to reestablish the giant section. Note the superficial location of DCIS and the distribution of AH and EH in proximity to DCIS. Star: area of sclerosing adenosis, curved arrow: knife mark for orientation of the small section. (C) A high magnification of the area of DCIS in B. Inset: a higher magnification of DCIS.

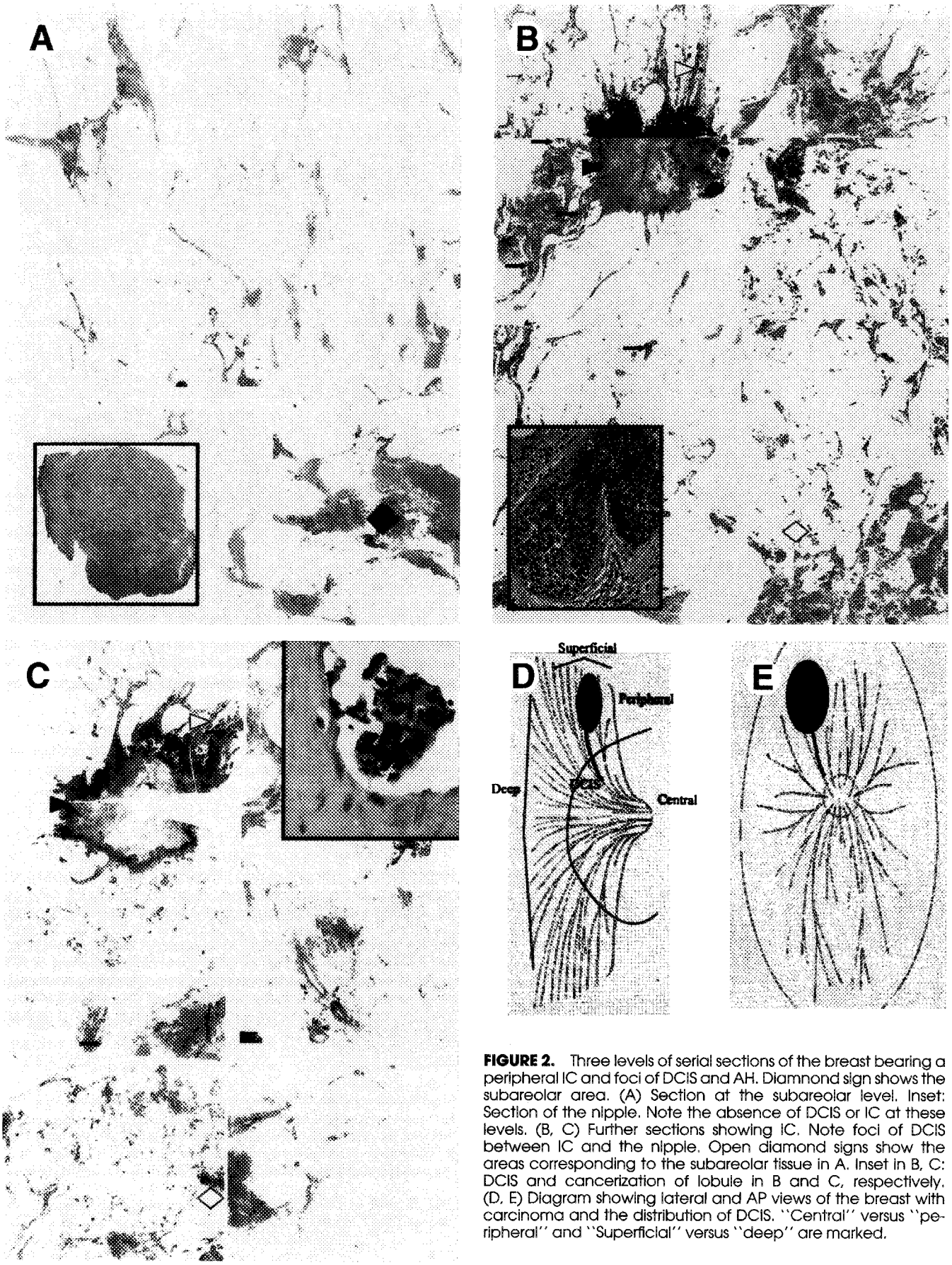

FIGURE 2. Three levels of serial sections of the breast bearing a peripheral IC and foci of DCIS and AH. Diamnond sign shows the subareolar area. (A) Section at the subareolar level. Inset: Section of the nipple. Note the absence of DCIS or IC at these levels. (B, C) Further sections showing IC. Note foci of DCIS between IC and the nipple. Open diamond signs show the areas corresponding to the subareolar tissue in A. Inset in B, C: DCIS and cancerization of lobule in B and C, respectively. (D, E) Diagram showing lateral and AP views of the breast with carcinoma and the distribution of DCIS. "Central" versus "peripheral" and "Superficial" versus "deep" are marked.

of areas containing portions of duct transitional between the DCIS and the benign duct epithelium. Using Adobe Photoshop version 3.0 software program, the glass slides were scanned with a photo scanner (Polaroid Sprint Scan)[23] with panel control setting as follows: "general-over exposure" for film, "color" for image type, and resolution of 253 (lowest resolution to minimize the size in bytes of the final composite computer image). The color and brightness of the image was enhanced (from 50% to 80%—the predominantly fatty tissue requiring highest degree of enhancement) by using the contrast-adjust icon in the image tool bar. Proper orientation of the section was performed by using the rotate canvas icon. The obtained image from Photoshop was transferred to the Microsoft PowerPoint—version 97. The images were assembled to reestablish the giant section and proportionally adjusted in size so that the giant section fit into the frame of the PowerPoint slide. The 3D structure of the breast was visualized by viewing the successive 2-dimensional image of the giant sections. Foci of DCIS, AH, and EH were counted on each giant sections.

The status of positive extensive intraductal component was defined using the criteria of the Joint Center for Radiation Therapy, Harvard Medical School, Boston, Massachusetts.[1] The location of the carcinoma was defined as follows: (1) superficial (near to the subcutaneous tissue) versus deep, and (2) peripheral (nearer the chest wall skeletal muscles than the nipple) versus central (nearer to the nipple than the chest wall skeletal muscles) (Fig 2). The size of the IC (greatest diameter) was measured on the reconstructed giant section. The extent of AH and marked EH was arbitrarily graded as follows: marked: >5 foci; moderate: 3 to 4 foci; mild: 1 to 2 foci.

RESULTS

The number of coronal slices of fresh breast varied from 3 to 7 (mean, 4). The number of slides varied from

TABLE 1. The Extent of DCIS (Case 1: Highest, Case 30: Absent), Status of Epithelial Hyperplasia, and Other Pathological Findings

Cases	Figure	Age	Size of IC (cm)	Location	Skip Areas of DCIS	Extent of DCIS: Central to IC*	Extent of DCIS: Peripheral to IC	AH	Marked EH
Positive EIC									
1		59	1.8	S, p	No	Paget's	No	Marked	Marked
2		70	0.3	S, p	Yes	1.5cm	No	Marked	No
3		45	2.0	S, p	No	Nipple	No	Mild	No
4	4	50	1.0	S, p	Yes	Subareolar	Yes	Moderate	Mild
5†		62	2.5, 5	S, p	No	1cm	No	Mild	Mild
6		62	3.0	D, p	No	1cm	No	Moderate	Mild
7†	5	59	2.5	S, p	No	Paget's	Yes	Mild	Moderate
8		44	0.5	S, p	No	2.5cm	No	Mild	Mild
9		73	1.0	S, p	No	2cm	No	Mild	Mild
10		58	2.5	S, c	No	Nipple	No	Mild	Mild
Moderate extent of DCIS outside IC									
11		59	2.0	S, c	No	1cm	Yes	Moderate	Mild
12		54	1.5	S, p	Yes	2cm	No	Mild	No
13		60	1.5	S, c	Yes	2.5cm	Yes	No	No
14	2	49	2.3	S, p	No	2.5cm	No	Mild	No
15		50	2.0	S, p	No	1cm	No	No	No
16		58	0.5	S, p	No	2cm	No	Marked	Moderate
17	6	71	2.7	S, p	Yes	1.5cm	No	Moderate	Moderate
Mild extent of DCIS outside IC									
18†	7	64	2.0‡, . .	S, p	No	Nipple	No	Mild	Mild
19		55	1.0	S, p	Yes	1cm	No	Mild	No
20		54	3.0	S, p	No	0.5cm	No	Mild	No
21	3	55	3.0	D, c	No	0	No	No	Marked
22		60	2.5	S, p	No	1.5cm	No	No	Mild
23		65	2.0	S, p	No	0.5cm	No	Mild	No
24	1	67	0.0	S, p	No	NA	NA	Moderate	Moderate
25		62	2.7	S, p	No	1cm	No	No	No
26		57	3.0	S, p	No	1cm	No	No	No
27		69	1.0	S, p	No	0	No	No	No
28		70	2.0	S, p	No	0	No	No	No
No DCIS									
29		52	1.5	S, p	No	0	No	No	No
30		53	1.5	S, p	No	0	No	No	Mild
Summary of cases		Mean: 61	Mean: 1.7	p: 26 c: 4	Nipple and subareolar tissue involved: 7		Yes: 4	No: 10	No: 14

NOTE. Extent of AH and marked EH was arbitrarily graded as follows: Marked: >5 foci; Moderate: 3-4 foci; Mild: 1-2 foci.

Abbreviations: S, superficial; D, deep; p, peripheral; c, central; NA, not available.

*The extent of DCIS central to the IC (in the breast tissue between the nipple and IC) was recorded as the spread of DCIS from the IC up to the subareolar tissue of the nipple (with or without Paget's disease) or as the greatest distance of spread from the border of the IC.

†Two or more duct systems involved by DCIS.

‡Three tumors measuring 2.0, 1.0, and 0.5 cm.

30 to 90 (mean, 45). The time for scanning glass slides and reassembling computer image of each slide into an image of a giant section was 2 to 4 hours.

Table 1 shows the distribution and extent of DCIS (in decreasing extent) and AH outside the infiltrating carcinoma (IC), and the sizes of IC. One case consisted only of DCIS (Fig 1, case 24), and 2 cases consisted only of IC (cases 29 and 30).

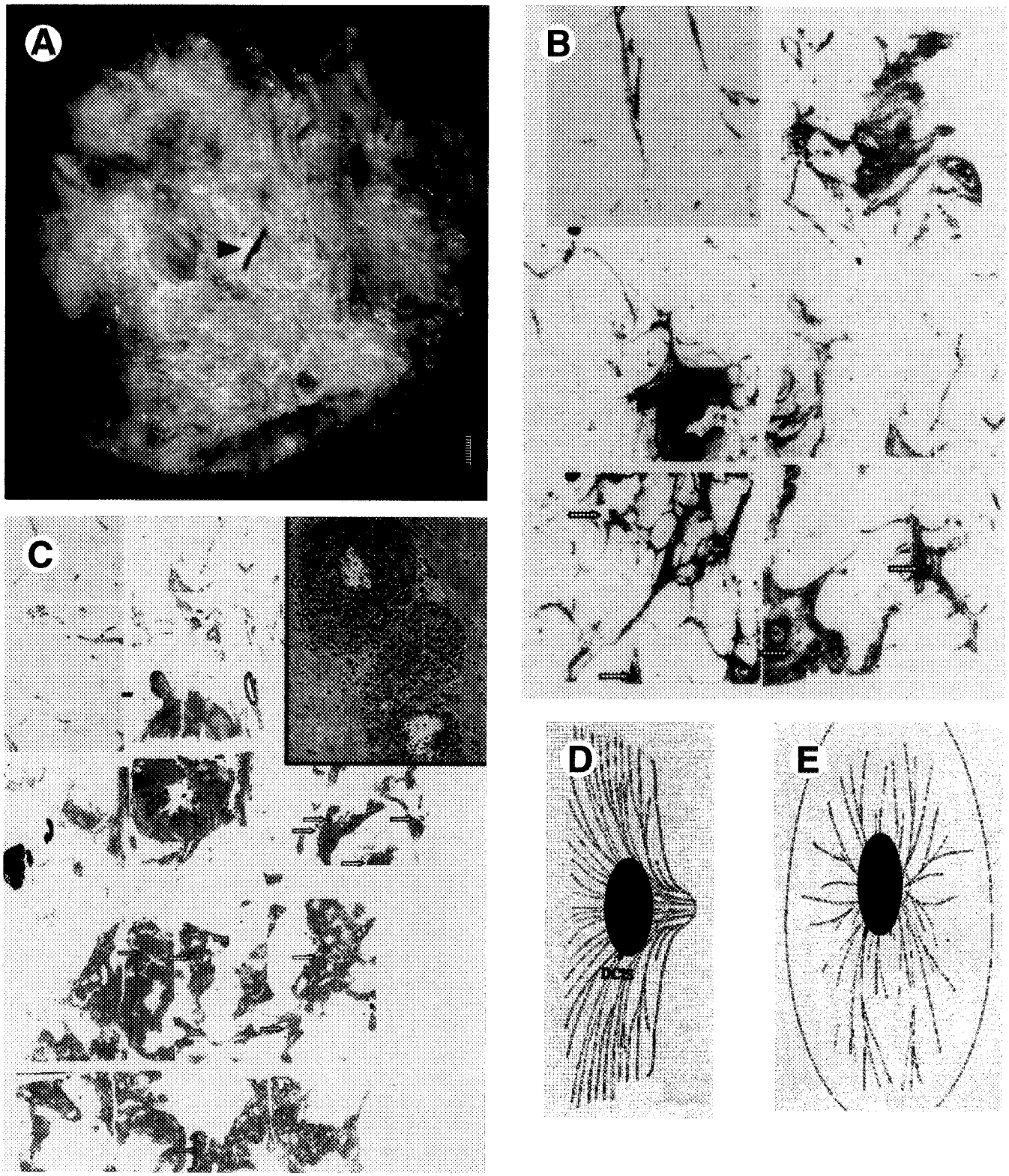

FIGURE 3. Two levels of sections of the breast having a deep IC with multiple foci of marked EH. (A, B) Coronal cross section showing the carcinoma in the deep breast tissue. Note the presence of a lymph node on the left side. (C) Coronal section next to B) with curved arrow showing a lymph node. Inset: A high magnification of an area with marked epithelial hyperplasia (open arrows). (D, E) Diagram showing lateral and AP views of the breast with carcinoma and the distribution of DCIS.

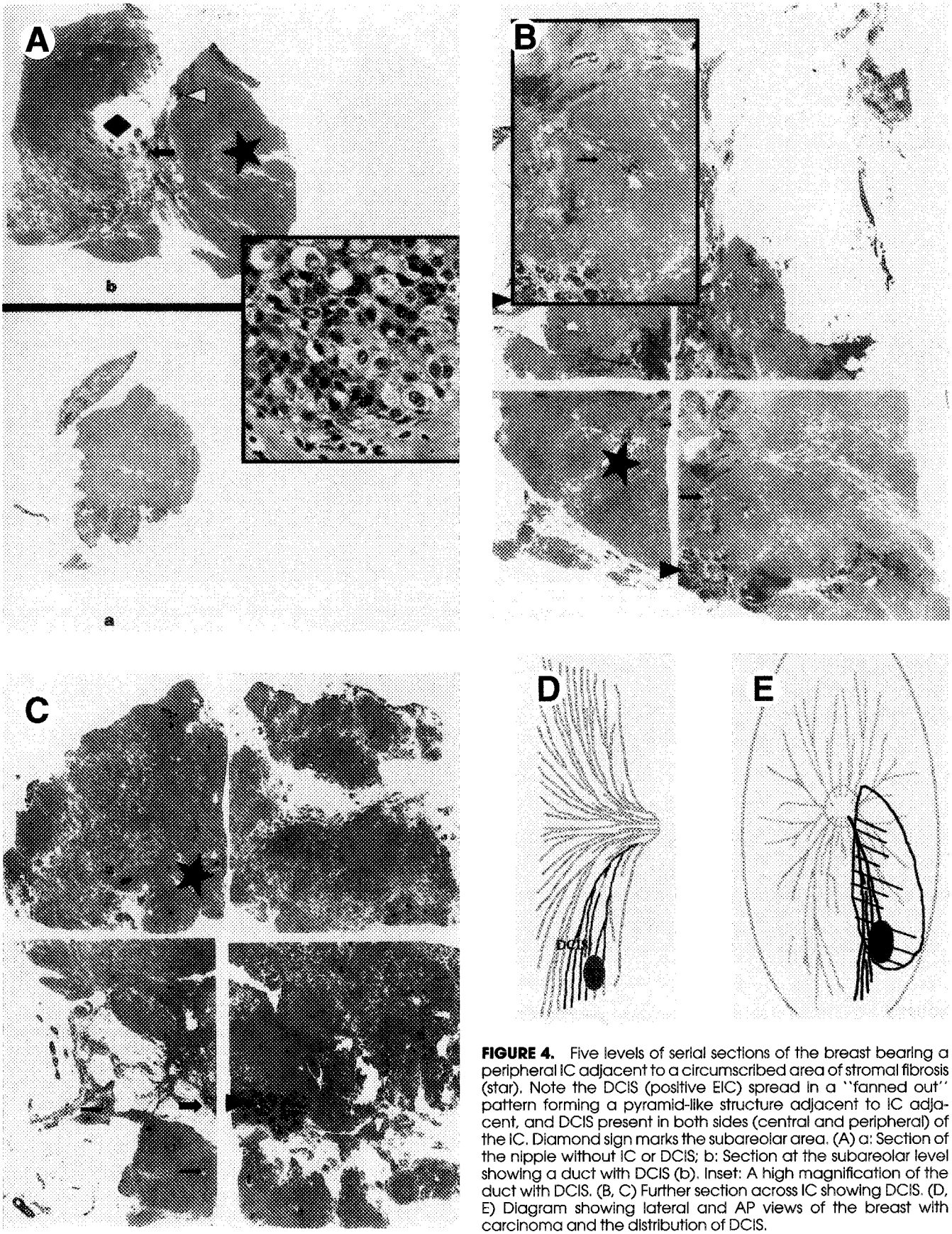

FIGURE 4. Five levels of serial sections of the breast bearing a peripheral IC adjacent to a circumscribed area of stromal fibrosis (star). Note the DCIS (positive EIC) spread in a "fanned out" pattern forming a pyramid-like structure adjacent to IC adjacent, and DCIS present in both sides (central and peripheral) of the IC. Diamond sign marks the subareolar area. (A) a: Section of the nipple without IC or DCIS; b: Section at the subareolar level showing a duct with DCIS (b). Inset: A high magnification of the duct with DCIS. (B, C) Further section across IC showing DCIS. (D, E) Diagram showing lateral and AP views of the breast with carcinoma and the distribution of DCIS.

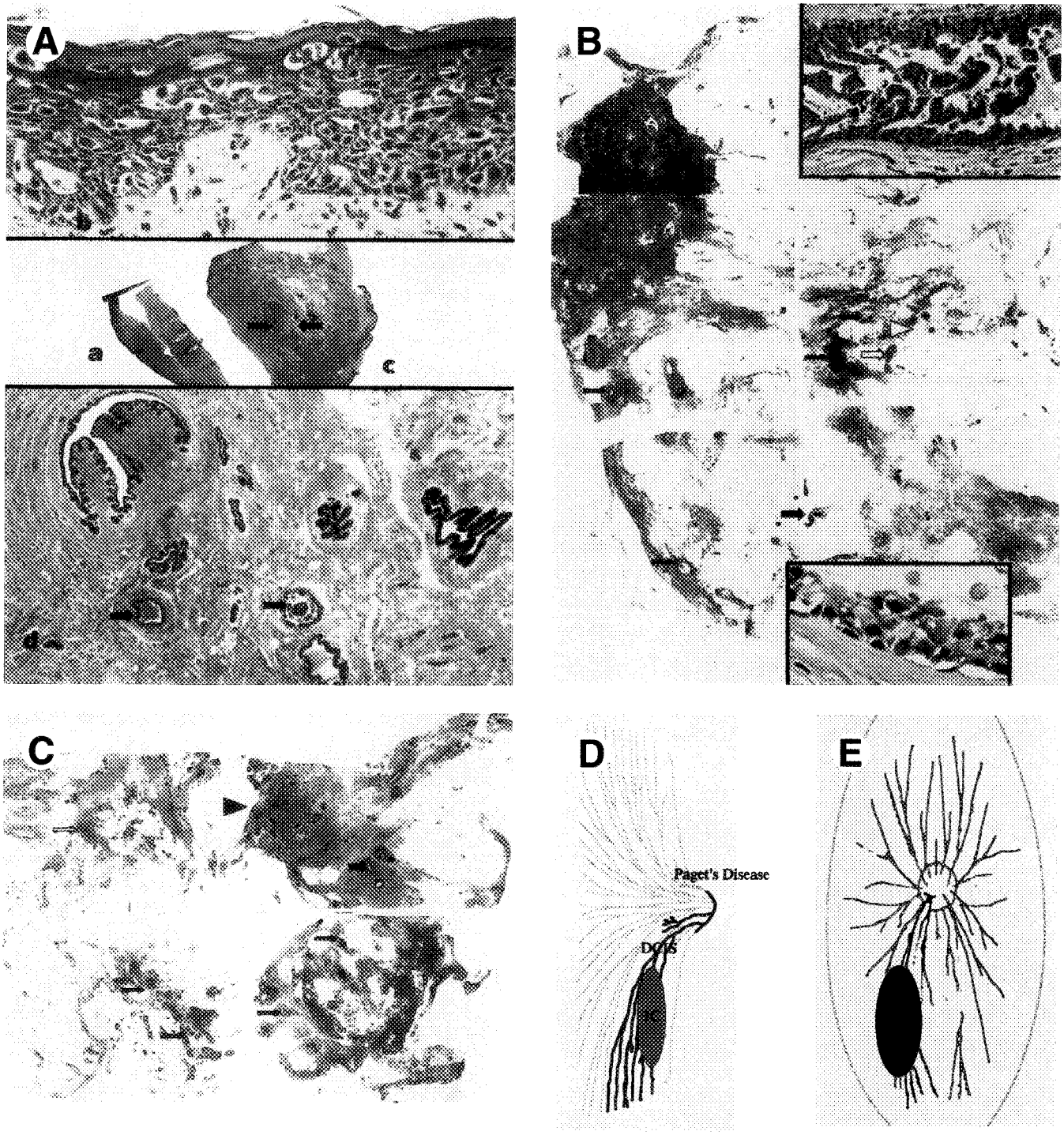

FIGURE 5. Four levels of sections of the breast with Paget's disease involving 2 adjacent lactiferous ducts. The superficial duct led to a superficial and peripheral IC and adjacent area of pure DCIS (positive EIC). The other deep duct led to a deep and central area of DCIS without IC. (A) (a, b) Section perpendicular to the skin showing Paget's disease; (c, d) cross section of the nipple showing 2 lactiferous with DCIS. (B) Further cross section of the superficial IC showing DCIS adjacent to IC and a second area of DCIS in the deep location. Inset a: DCIS of the central area; Inset b: DCIS of the superficial area. (C) Section between the edge of IC and the deep resection margin shows the tumor spread pattern of the superficial area of DCIS in B. (D) Diagram showing lateral and AP views of the breast with carcinoma and the distribution of DCIS.

The carcinoma was seen located in the superficial breast segment in 28 cases (Fig 2, case 14) and in the deep segment in 2 cases (cases 6 and 21) (Fig 3, case 21). In the serial coronal sections of the breast, the carcinoma was found to be located in areas corresponding to the same segment of breast (Figs 2—case 14, 4—case 4, 5—case 7). In the nipple, the lactiferous duct with DCIS corresponding to the breast segment with superficial carcinoma was also identified in the superficial location (Fig 5).

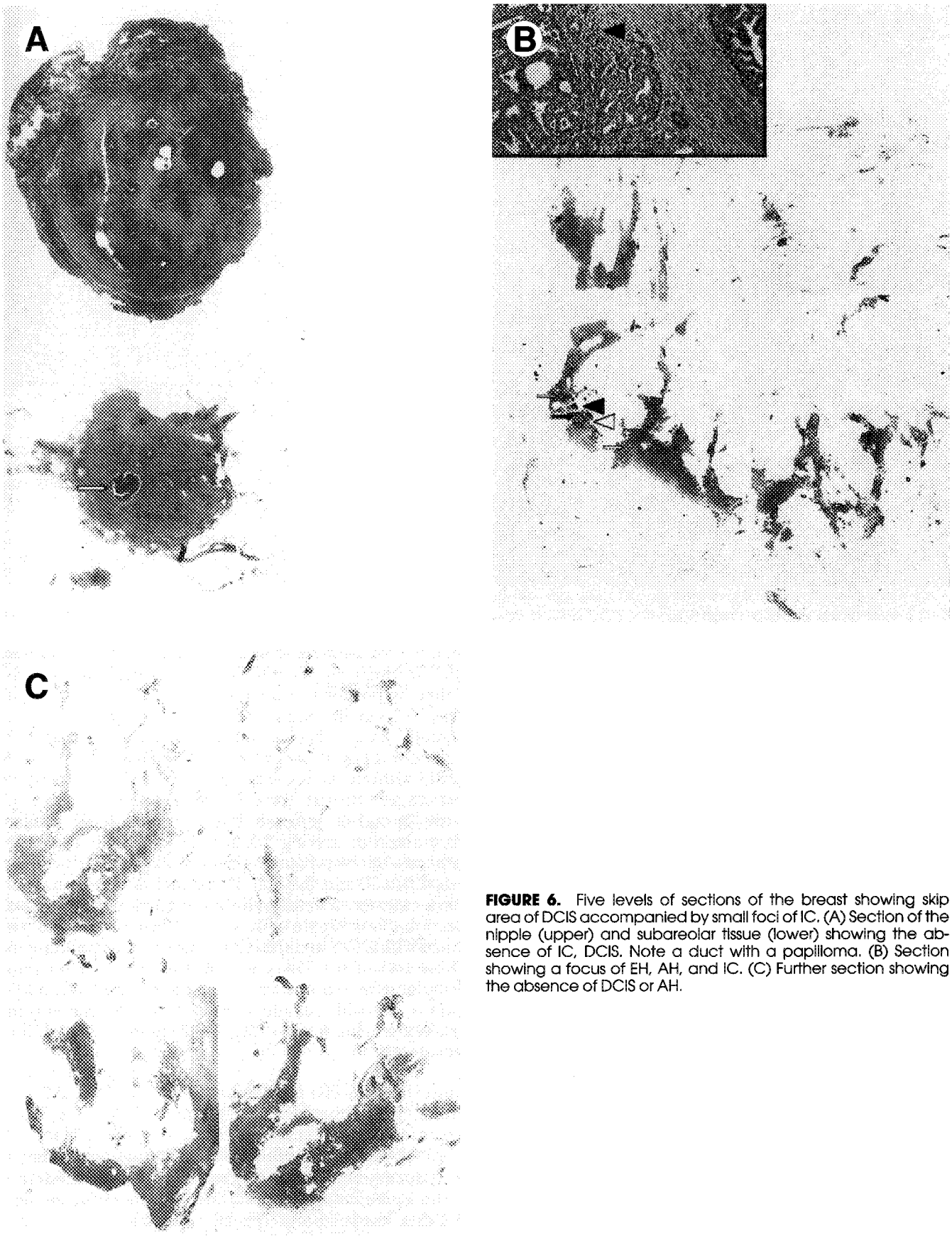

FIGURE 6. Five levels of sections of the breast showing skip area of DCIS accompanied by small foci of IC. (A) Section of the nipple (upper) and subareolar tissue (lower) showing the absence of IC, DCIS. Note a duct with a papilloma. (B) Section showing a focus of EH, AH, and IC. (C) Further section showing the absence of DCIS or AH.

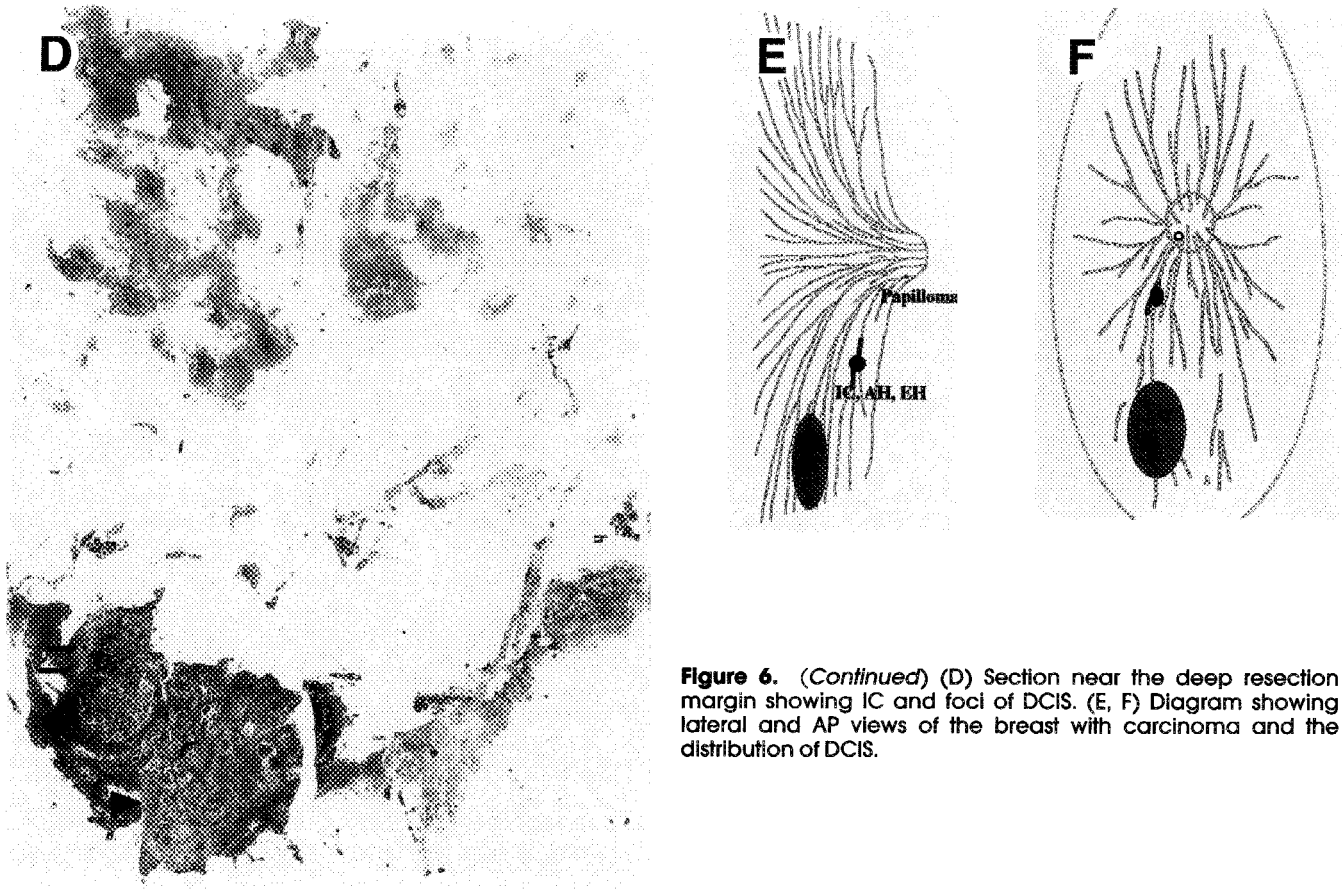

Figure 6. (*Continued*) (D) Section near the deep resection margin showing IC and foci of DCIS. (E, F) Diagram showing lateral and AP views of the breast with carcinoma and the distribution of DCIS.

Ducts with DCIS, in either a continuous or discontinuous pattern of spread, were disposed in a "fanned out pattern." This pattern of spread formed a pyramid-like structure with the summit toward the nipple and the base facing the chest wall (Figs 4, 5). The IC were peripheral in 26 cases and central in 4 cases (cases 6, 10, 13, and 21), including the case with deep carcinoma (case 6).

The IC with DCIS was identified in the area adjacent to the area of pure DCIS (Figs 4, 5). None of the cases of IC was seen surrounded by DCIS. Epithelial hyperplasia with or without atypia was often identified in areas adjacent to DCIS (Figs 1C, 5B, and 6B). Sections of the breast tissue between the IC and the deep resection margin of the mastectomy specimen showed DCIS in 4 cases (2 central carcinomas—cases 11 and 13—and 2 peripheral carcinomas—cases 4 and 7) (Figs 4, 5). Breast tissue between the nipple and the IC showed the presence of DCIS in most of those cases having both components of carcinoma (24 cases). The extension of DCIS toward the nipple ranged from cases with DCIS present only at the edge of the IC to cases with DCIS extending to the nipple with or without Paget's disease. Five peripheral carcinomas and 1 central carcinoma were associated with intraductal carcinoma with (cases 1 and 7) or without Paget's disease (cases 3, 4, 10, and 18) in the nipple or subareolar tissue.

Multiple foci of DCIS could be seen to be connected in the serial sections. However, at least 6 cases had low- or high-grade DCIS (cases 2, 4, 12, 13, 17, and 19) in which the foci DCIS were separated from each other by portions of duct with benign epithelium (at least 0.3 cm in length) (Fig 6). One case of Paget's disease (case 7, Fig 5) had 2 lactiferous ducts from 2 separate areas of breast affected by DCIS and IC and DCIS without IC, respectively. In another 2 cases without Paget's disease (cases 5 and 18) (Fig 7; case 18). Case 6 had 2 separate but histopathologic similar carcinoma measuring 2.5 and 0.3 cm. Case 18 had 3 separate but histopathologically similar tumors measuring 2.0, 1.0, and 0.5 cm. These foci of carcinomas in each case were located in different quadrants. The cross section of the nipple in these cases showed 3 lactiferous ducts with DCIS in different locations corresponding to these foci of IC. There was no tumoral invasion into lymphatic or vascular vessels in these 2 cases. In addition, 1 case with a single focus of IC was associated with multiple foci of marked EH in different quadrants (Fig 3; case 21).

DISCUSSION

The clinical significance of DCIS and AH has been well documented in the literature.[1-8] DCIS is considered to be a precursor of most IC and the cause of recurrent IC after lumpectomy, especially if it involves the resection margin.[24,25] In addition, DH is considered a weaker marker of breast carcinoma, arising in either the same

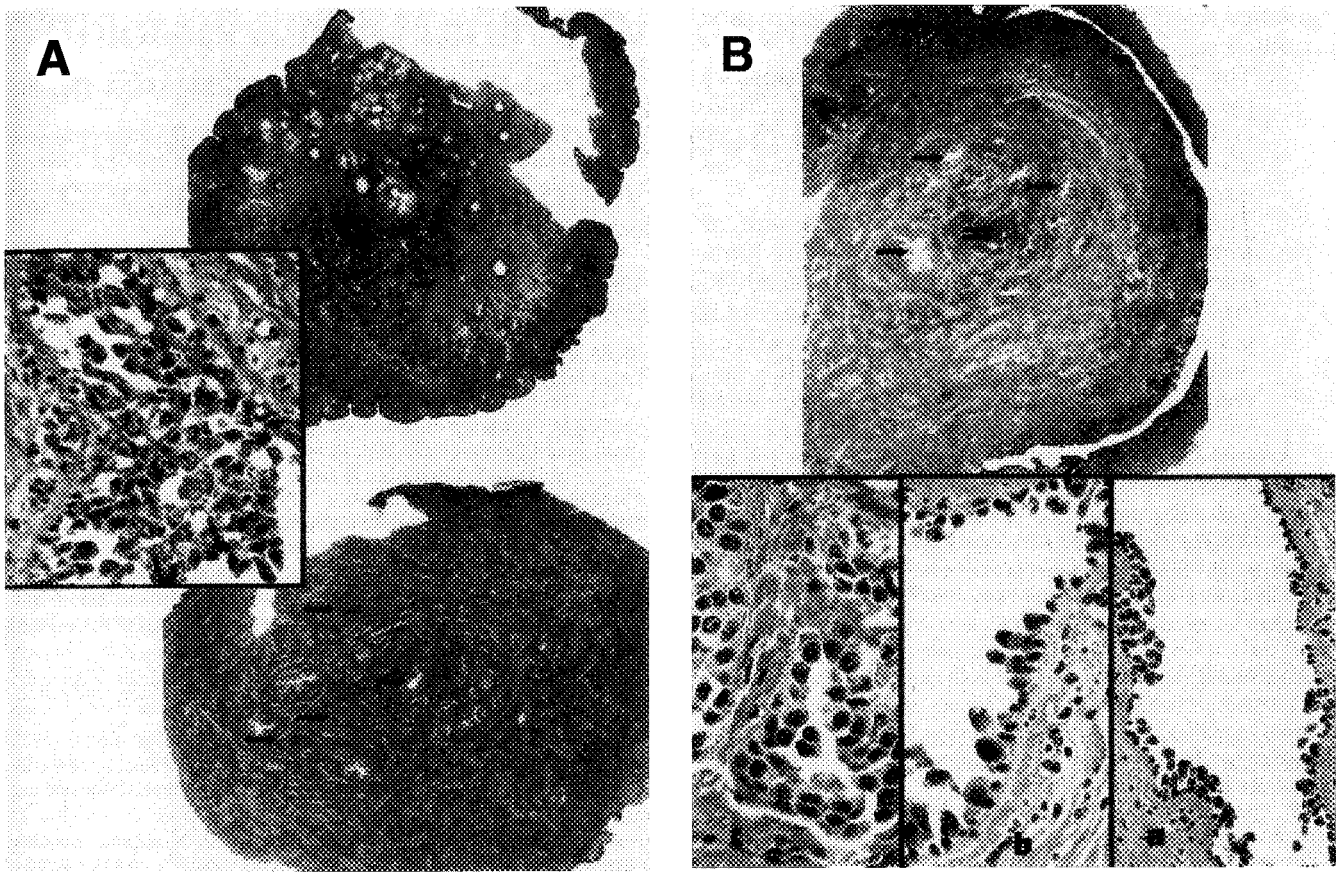

FIGURE 7. Three levels of sections in a case with 4 lactiferous ducts having DCIS without Paget's disease, associated with 3 separate superficial foci of IC in 3 different quadrants. The continuous or discontinuous DCIS spread pattern could not be verified. (A) Upper: Superficial section of the nipple showing no DCIS. Lower: Deeper section of the nipple showing 4 lactiferous ducts with DCIS. Inset: A duct with DCIS. (B) Section of the subareolar level showing 4 ducts with DCIS. Inset a: Representative section of the IC in the peripheral breast tissue. Inset b, c: Representative areas of DCIS in 2 separate lactiferous ducts.

quadrant as the DH, a different quadrant, or even the contralateral breast.[1]

In this study of the 3D structure of the breast bearing IC less than 3 cm in diameter, the geographic distribution of DCIS in areas likely confined to a segment of breast. This segment of breast involved by the carcinoma appears to arise from ducts and acini belonging to the same lactiferous duct system. This impression was based on the following observations:

1. Connections between different foci of DCIS
2. The location of DCIS in the same areas of the same duct system at different levels of coronal sections
3. The "fanned out" pattern of DCIS, consistent with the pattern of branching of the main lactiferous ducts

The close association of marked DH and ADH with DCIS as described in this study suggests that these lesions were likely located in the same segment of breast as the carcinoma. The size and extent of DCIS in a number of cases in this study account for the increase in volume of the involved breast segment. Extension of DCIS into an adjacent segment through ductal anastomoses[22] cannot be completely excluded; however, such anastomoses were not evident in this study. Our findings support the notion that carcinoma is usually confined to a single duct system.[14,15,26] It is also likely that the case of Paget's disease associated as it was with 2 separate foci of DCIS involving 2 separate lactiferous ducts, represents a continuous spread of tumor from 1 duct system to another duct system, possibly through the epidermis with Paget's disease. The pattern of spread in DCIS has been described as continuous or discontinuous.[14,15,19] Spread was found to be continuous in cases of high-grade DCIS, and continuous or discontinuous in cases of low-grade tumor.[15] In our study, discontinuous DCIS spread within the duct system was not uncommon and was also identified in high-grade DCIS. This pattern of discontinuous spread of DCIS may be attributed to (1) multicentricity/multifocality phenomenon or (2) tumor implantation. Furthermore, 2 cases with multiple foci of IC and a case with multiple foci of marked epithelial hyperplasia in different quadrant also represent the "skip area" phenomenon with neoplastic lesions arising in different duct systems.

The high prevalence of DCIS restricted to a single duct system is probably at the root of good results seen in cases of breast carcinoma treated with segmental resection. Failure of the complete removal of tumor in

segmental resections for small breast carcinoma may be attributed to

1. The "fanned out" pattern of DCIS resulting in a pyramid-like shape of DCIS in the more peripheral and superficial or deep breast tissue
2. The frequent extension of DCIS centrally toward the nipple
3. The localization of IC and DCIS. IC with or without DCIS is not surrounded by its intraductal component but is located adjacent to area of DCIS (without IC). Because IC is readily palpable, failure of the intraoperative identification of DCIS that is not readily palpable may result in inadequate excision of the carcinoma.

Acknowledgment The authors thank D. Brazeau for her secretarial assistance, all histotechnologists, and pathologist assistants at the Anatomical Pathology Laboratory of the Ottawa Hospital, Civic Campus, for their technical work, and R. Elford, Biomedical Communications of the Ottawa Hospital, Civic Campus, for his printing of computer images.

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